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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,807	07/05/2001	Peng Huang	UTSC:618US	9670

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,807	HUANG ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-35 and 37-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *6,11,13,19,24,26,41 and 46* is/are allowed.

6)☐ Claim(s) *1-5, 7-10, 12, 14-18, 20-23, 25, 27-40, 42-45, 47-52,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 and 37-52 are pending. After review and reconsideration, the Office action mailed August 11, 2003 is vacated and the Election of Species requirement, mailed October 2, 2002 is withdrawn in order to advance prosecution..

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The rejection of claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) in view of Mukhopadhyay et al (U.S. 5,958,892, reference A14 of the IDS filed October 16, 2001) is maintained for reasons of record..

Claim 1 is drawn to a method of killing a cell comprising contacting a cell with a first composition comprising an agent that increases intracellular superoxide, and contacting said cell with a second composition comprising 2-methoxyestradiol. Claim 2 embodies the method of claim 1 wherein said cell is a cancer cell. Claim 3 specifies that said cancer cell be derived from a solid tumor. Claim 4 embodies the method of claim 1 wherein said cell is a human cell. Claim 12 embodies the method of claim 1, wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 14-16 embody the method of claim 1 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 17 embodies the method of claim 1 wherein said first and second compositions are combined in a single formulation.

Claim 18 is drawn to a method of treating cancer comprising administering to a host a composition comprising 2-methoxyestradiol and an agent which increases intracellular superoxide. Claim 25 embodies the method of claim 18 wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 28-30 embody the method of claim 18 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 31 embodies the method of claim 18 wherein said first and second compositions are combined in a pharmaceutically acceptable composition. Claim 32 specifies that the pharmaceutically acceptable composition

includes a pharmaceutically acceptable carrier. Claims 33-35 embody the method of claim 31, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, and injection, respectively. Claim 36 embodies the method of claim 18 wherein the host has cancer. Claims 37 and 38 specify a solid tumor and leukemia, respectively. Claim 39 embodies the method of claim 18 wherein the first and second compositions are combined in a single formulation.

Claim 40 is drawn to a composition comprising 2-methoxyestradiol and a second compound which increases intracellular superoxide. Claim 45 specifies that the agent that increases intracellular superoxide comprises an arsenate. Claim 47 embodies the composition of claim 40 wherein said composition is a pharmaceutically acceptable composition.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity in a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach pharmaceutical composition comprising arsenates and pharmaceutically acceptable carriers and methods of treatment comprising oral, parenteral and injection administration of said arsenates (column 5, line 51 to column 6, line 41). Uckun et al teach that the compositions and methods are effective at inducing apoptosis in cancer cells and can be administered to a human patient (column 5, lines 52-54). Uckun et al do not teach the combination of the arsenate compounds with 2-methoxyestradiol, or increasing intracellular superoxide by the administration of the arsenate compounds.

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis in cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with at least one chemotherapeutic agent (column 20, lines 54-67). Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al teach the a single composition or pharmaceutical formulation that comprises both agents, or the administration of both agents, in distinct compositions at the same time. Mukhopadhyay et al teach that the treatment with 2-methoxyestradiol may precede or follow the treatment with the chemotherapeutic agent (column 21, lines 5-39), thus fulfilling the specific embodiments of claims 14-17 and 28-32 and 39.

Mukhopadhyay et al do not specifically teach the combination of 2-methoxyestradiol with an arsenate agent.

The instant situation is amenable to the type of analysis set forth In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose In order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually in the prior art. Applying the same logic to the instant method and composition claims, given the teaching of the prior art of methods of inducing apoptosis In solid tumor by the administration of 2-methoxyestradiol as taught by Mukhopadhyay et al and the method of inducing apoptosis In a solid tumor by the administration of the arsenate compounds of Uckun et al, it would have been obvious to combine both 2-methoxyestradiol and arsenates for the treatment of solid tumors because the idea of doing so would have logically followed from their having been individually taught In the prior art to be useful as agents for treating tumors by the induction of apoptosis In tumor cells. Furthermore, It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine administration of arsenate with administration of 2-methoxyestradiol.. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the combination of 2-methoxy estradiol with other chemotherapeutic agents and the teachings of Uckun et al on arsenates as chemotherapeutic agents. Although neither reference teaches that arsenate compounds increase intracellular superoxide levels, there would be motivation to combine both 2-methoxyestradiol and the arsenate compounds taught by Uckun et al for the reasons set forth above. Therefore, the increase in intracellular superoxide levels, although not relied upon to render obvious the combination, would be inherent in the combined method.

The rejection of claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) In view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al (Toxicology and Applied Pharmacology,

!999, Vol. 159, pp. 65-75) is maintained for reasons of record. The embodiments of the claims are set forth above.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity In a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach pharmaceutical composition comprising arsenates and pharmaceutically acceptable carriers and methods of treatment comprising oral, parenteral and injection administration of said arsenates (column 5, line 51 to column 6, line 41). Uckun et al teach that the compositions and methods are effective at inducing apoptosis In cancer cells and can be administered to a human patient (column 5, lines 52-54). Uckun et al do not teach the combination of the arsenate compounds with 2-methoxyestradiol.

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis In cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with hydrogen peroxide (column 20, lines 54-67 and column 21, lines 58-61). Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al teach the a single composition or pharmaceutical formulation that comprises both agents, or the administration of both agents, In distinct compositions at the same time. Mukhopadhyay et al teach that the treatment with 2-methoxyestradiol may precede or follow the treatment with the chemotherapeutic agent (column 21, lines 5-39), thus fulfilling the specific embodiments of claims 14-17 and 28-32 and 39. Mukhopadhyay et al do not specifically teach the combination of 2-methoxyestradiol with an arsenate agent.

The abstract of Barchowsky et al teaches that vascular endothelial cells exhibited increased superoxide and hydrogen peroxide accumulation when exposed to low levels of arsenic.

It would have been prima facie obvious to one of ordinary skill In the art at the time the claimed invention was made to administer 2 methoxyestradiol and arsenate In a method of treating cancer In a host and a method of killing a cell. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the efficacy of combining treatment with 2-methoxyestradiol with

hydrogen peroxide, and the teachings of the abstract of Barchowsky et al regarding increased superoxide and hydrogen peroxide accumulation In vascular endothelial cells exposed to arsenic.

Although neither Mukhopadhyay et al nor Uckun et al teach the necessity of increasing intracellular superoxide levels, there would be motivation to combine both 2-methoxyestradiol and the arsenate compounds taught by Uckun et al because Mukhopadhyay et al teaches the combination with hydrogen peroxide and Barchowsky et al teaches that arsenic exposure causes an accumulation of hydrogen peroxide. Therefore, the increase In intracellular superoxide levels, although not relied upon to render obvious the combination, would be inherent In combined method as evidenced by Barchowsky et al.

The rejection of claims 1-5, 12, 14-18, 25, 27-40, 45 and 47 under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) In view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al as applied to claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 in the section above, and further in view of the abstract of Oldham et al (Proceed Amer Assoc Cancer Res, 2000, Vol. 41, page 766, reference C23 of the IDS filed October 16, 2001) is maintained for reasons of record. The embodiments of claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 are set forth, above.

Claim 4 is drawn to the method of claim 2 wherein said cancer cell is a leukemia cell. Claim 38 is drawn to the method of claim 36, wherein said cancer is leukemia.

The combination of Uckun et al and Mukhopadhyay et al and the abstract of Barchowsky et al render obvious claims 1-3, 5, 12, 14-18, 25, 27-37, 39, 40, 45 and 47 for the reasons set forth in the section above.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity In a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach that the compositions and methods are effective at inducing apoptosis In cancer cells (column 5, lines 52-54).

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis In cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach

that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al do not teach a method for treating leukemia comprising the administration of 2-estradiol.

The abstract of Oldham et al teaches that 2-methoxy estradiol selectively kills leukemia cells and that this killing is a result of inhibition of superoxide dismutase by 2-methoxyestradiol. The abstract further teaches that superoxide dismutase is a key enzyme responsible for protecting cells from free-radical damage due to superoxide radicals.

It would have been prima facie obvious to one of ordinary skill In the art at the time the claimed invention was made to administer 2 methoxyestradiol and arsenate In a method of treating leukemia and a method of killing a leukemia cell. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the efficacy of combining treatment with 2-methoxyestradiol with hydrogen peroxide, and the teachings of the abstract of Barchowsky et al regarding increased superoxide and hydrogen peroxide accumulation in vascular endothelial cells exposed to arsenic, and the abstract of Oldham et al on the selective killing of leukemia cells taken from patients by 2-methoxyestradiol, wherein the 2-methoxyestradiol inhibited superoxide dismutase. One of skill In the art would be motivated to combine 2-methoxyestradiol and arsenate In order to inhibit superoxide dismutase by 2-methoxyestradiol and then increase the level of superoxide radicals by the administration of arsenates.

Applicant has submitted the Declaration of Kevin Casement under 37 CFR 1.132 to aver that Mukhopadhyay et al (U.S. 5,958,892) was commonly owned at the time of filing and therefore is not available as a reference under 35 USC 103(a). This has been considered but not found persuasive to overcome the 103(a) rejection because the '892 patent qualifies under 35 U.S.C as 102(a).art being published before the filing date of the instant application.

Applicant has submitted the Declaration of inventors Huang, Plunkett and Feng to aver that the instant invention was reduced to practice prior to June 23, 1999 in order to swear behind the teachings of Uckun et al (U.S. 6,191,123). This has been considered but found not to be sufficient to antedate the '123 patent. Firstly, the '123 patent has priority to provisional application 60/125,337, filed March 19, 1999, therefore the statement that the instant invention

was reduced to practice before June 23, 1999 is insufficient to antedate the instant invention. Secondly, the evidence presented in the exhibit filed May 16, 2003 is not persuasive. The provided text refers to the compound "MDA-CMP1". Such a compound is not known in the art as of the filing date sought, and the exhibit does not provide a structure for MDA-CMP1, stating only that it is a human steroid metabolite that selectively inhibits SOD leading to oxidative stress. The exhibit contemplate use of this compound to enhances the effectiveness of "radiotherapy and other anticancer agents which generate free radicals in cells". However, there is no contemplate of the co-administration of an agent which increases intracellular O2 radicals. The statement of "free radicals" does not define the specific population of radicals. Further there is no contemplation of the specific combinations claimed, requiring rotenone, bleomycin, daunorubicin, epirubicin, TNF-alpha, , heat, arsenate, or a retinoic acid derivative.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 18, 27, 37, 40 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Mukhopadhyay et al (WO 98/04291)..

Mukhopadhyay et al disclose a method of treating a solid tumor such as a sarcoma, breast cancer or lung tumor (claims 5-8) comprising the administration of 2-meethoxyestradiol and a DNA damaging agent such as hydrogen peroxide (page 39, line 30 to page 40, line 1). Hydrogen peroxide fulfill the specific embodiment of an agent which increases the level of oxygen radicals in the cell.

Claims 1-3, 5, 7-9, 14, 17, 18, 20-22, 27, 28, 31, 32-37, 39, 40, 42-44 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mukhopadhyay et al (WO 98/04291) in view of Wang et al (U.S. 5,843,459) and

Mukhopadhyay et al teach a method of treating a solid tumor such as a sarcoma, breast cancer or lung tumor (claims 5-8) comprising the administration of 2-meethoxyestradiol and a DNA damaging agent such as chemotherapeutics (page 39, line 30 to page 40, line 1).

Wang et al teach that bleomycin, duanorubicin and epirubicin induce DNA damage (column 3, lines 15, 17 and 18). The art teaches that bleomycin, daunorubicin and epirubicin are chemotherapeutic agents (du Bois et al, Journal of Clinical Oncology, 1999, Vol. 17, pp. 46-51).

It would have been prima facie obvious at the time the claimed invention was made to use bleomycin, daunomycin or epirubicin in combination with 2-methoxyestradiol in the method of treatment taught by Mukhopadhyay et al. One of skill in the art would have been motivated to do so because bleomycin, daunomycin and epirubicin are chemotherapeutic agents which are DNA damaging agent as required by the method of Mukhopadhyay et al.

Claims 1-3, 5, 10, 14, 17, 18, 23, 27, 28, 31, 32-37, 39, 40 and 47-52 re rejected under 35 U.S.C. 103(a) as being unpatentable over Mukhopadhyay et al (WO 98/04291) in view of Carmine et al (Journal of Bioluminescence and Chemiluminescence, 1994, Vol. 9, pp. 267).

Mukhopadhyay et al teach a method of treating a solid tumor such as a sarcoma, breast cancer or lung tumor (claims 5-8) comprising the administration of 2-meethoxyestradiol and a DNA damaging agent such as hydrogen peroxide (page 39, line 30 to page 40, line 1). Mukhopadhyay et al teach a that the 2-methoxyestradiol is administered in conjunction with an agent that increases p53 expression in the cancer cell, and suggests that glioblastoma is a type of cancer which would be amenable to suppression by p53. Mukhopadhyay et al do not teach the administration of TNF-alpha and 2-meethoxyestradiol.

Carmine et al teach that recombinant tumor necrosis factor induces the formation of hydrogen peroxide by neuroblastoma cells in culture (Figure 4, page 271).

It would have been prima facie obvious at the time the invention was made, to substitute the administration of TNF-alpha for the administration of hydrogen peroxide in order to treat glioblastoma. One of skill in the art would have been motivated to do so by the teachings of Carmine et al who teach that TNF-alpha can induce elevated levels of TNF-alpha in a neuronal cell culture and the suggestion of Mukhopadhyay et al that the method can be applied to glioblastoma. One of skill in the art would be motivated to administer TNF alpha in place of an

intralesional injection of hydrogen peroxide in order to prevent damage to surrounding normal tissue from any diffusion of hydrogen peroxide from the tumor vasculature.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
10/16/2006